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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/291,894	04/13/99	COLLINS	P 17634-000520

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TOWNSEND AND TOWNSEND AND CREW
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EXAMINER	
BRUMBACK, B	
ART UNIT	**PAPER NUMBER**
1642	12

DATE MAILED: 03/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/291,894	Collins et al.
Examiner	**Group Art Unit**
Brenda Brumback	1642

☒ Responsive to communication(s) filed on *Jan 25, 2001*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-35 and 46-65* is/are pending in the application.

Of the above, claim(s) *13-15, 17, 22-34, and 60-63* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12, 16, 18-21, 35, 46-59, 64, and 65* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, claims 1-30, 35, and 46-65 and species 11, chimeric RSV with a G heterologous gene in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-35 and 46-65 are pending. Claims 31-34 are withdrawn from examination as directed to a non-elected invention. Claims 13-15, 17, 22-30, and 60-63 are withdrawn from examination as directed to non-elected species. Claims 1-12, 16, 18-21, 35, 46-59, and 64-65 are examined on the merits to the extent that they read on the elected species, human/human chimeric RSV with a G heterologous gene.

Information Disclosure Statement

3. The Information Disclosure Statements filed 02/01/2000 and 12/04/2000 have been considered. Signed copies of the PTO-1449 forms are attached hereto.

Claim Objections

4. Claim 35 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the

claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 35 is drawn to the chimeric respiratory syncytial virus of claim 1 "which is a virus"; as such, claim 35 does not further limit claim 1.

Claim Rejections - 35 USC § 112

5. Claims 5, 7, and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 5, 7, and 8 recite a chimeric RSV with a heterologous gene encoding a G glycoprotein or immunogenic epitope thereof. The disclosure fails to teach what is encompassed within the metes and bounds of an immunogenic epitope of RSV G protein; therefore, the metes and bounds of the claimed invention cannot be determined.

6. Claims 5, 7, and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for chimeric RSV with a heterologous gene encoding a G glycoprotein, cytoplasmic domain, transmembrane domain, or ectodomain, does not reasonably provide enablement for chimeric RSV with a heterologous gene encoding an immunogenic epitope of a G glycoprotein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the full scope of the claims for the following reasons:

The nature of the invention: The invention is drawn to chimeric RSV comprising a partial or complete RSV genome of one human RSV with a heterologous gene or gene segment of a different human RSV strain or subgroup, wherein the heterologous gene encodes a G

glycoprotein, cytoplasmic domain, transmembrane protein or immunogenic epitope thereof. While the disclosure teaches the G glycoprotein of each of the RSV A and B subgroups and teaches the cytoplasmic and transmembrane domains, it fails to teach immunogenic epitopes of the G glycoprotein.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the complete G glycoprotein is immunogenic, but does not teach immunogenic epitopes thereof (see for example, Oien et al., Vaccine 1993, 11 (10) p1040-8, especially the abstract).

The amount of direction or guidance present and the presence or absence of working examples: The specification teaches that the combination of the complete sequence of the G gene of one of the RSV subgroups with an RSV of the heterologous subgroup is immunogenic for the first subgroup; however, the specification does not teach epitopes of the G glycoprotein which can be combined with the heterologous subgroup virus in order to elicit an immunogenic response to the G glycoprotein of the first subgroup (see pages 200-213). The specification fails to provide any guidance as to how immunogenic epitopes of the G glycoprotein might be delineated for combination with a virus of the heterologous subtype. There are no working examples describing immunogenic epitopes and there is no guidance as to how one might determine which portions of the G glycoprotein could reasonably be expected to comprise immunogenic epitopes.

The breadth of the claims and the quantity of experimentation needed: Because the claims encompass immunogenic epitopes of the G glycoprotein and because neither the art not the disclosure teach what these immunogenic epitopes encompass, it would require undue

experimentation by one of skill in the art to be able to practice the claimed invention commensurate in scope with the claims.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ormum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12, 16, 18-21, 35, 46-59, and 64-65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 96-103, 131, and 151-153 of of copending Application No. 09/444,067 and claims 20, 31, and 56 of copending Application No. 09/444,221. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are drawn to chimeric human/human respiratory syncytial viruses of different subgroups (A and B) having a heterologous G gene .

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102/103

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 1-12, 16, 18-21, 35, 46-59, and 64-65 are rejected under 102(b) as anticipated by, or in the alternative, under 35 U.S.C. 103(a) as obvious over Randolf et al. (EPA 0 567 100).

The claimed invention is drawn to an isolated infectious chimeric respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, a RNA polymerase elongation factor, and a partial or complete genome of one human RSV strain (subgroup A) combined with a heterologous gene of a different RSV strain (subgroup B), wherein the heterologous gene is the G gene and wherein the chimeric

RSV is further modified by one or more attenuating mutations adopted from different biologically derived mutant RSV strains or stabilized by multiple nucleotide changes in the codon specifying the mutation, formulated in a dose of 10^3 to 10^6 PFU of attenuated virus. The claimed invention is also drawn to immunogenic compositions comprising the virus for administration to the upper respiratory tract by spray, droplet or aerosol and to isolated polynucleotides comprising a chimeric RSV genome or antigenome of one human RSV strain (subgroup A) combined with a heterologous gene of a different RSV strain (subgroup B), wherein the heterologous gene is the G gene.

Randolph et al. teach vaccine compositions comprising mutant RSV of subgroups A and B and nucleic acid molecules encoding the mutant RSV (see the abstract). Randolph et al. teach that both subgroups are important respiratory pathogens and suggest that an effective vaccine compositions should protect against both groups (see page 2, lines 12-30). Randolph et al. teach human chimeric RSV in which the nucleic acid regions encoding one or more polypeptides of one of the RSV types (A or B) is substituted into the genome of the heterologous type (see page 5, lines 50-53). Randolph teach the immunogenic polypeptides of RSV as the G polypeptide, among others (see page 4, lines 32-33, and page 6, lines 3-4). Randolph teach the RSV as further comprising the N protein, the P protein, the L protein, and regulatory sequences (see page 4, lines 32-33, and page 5, lines 44-49). Randolph et al. teach the RSV as also comprising one or more attenuating mutations adapted from biologically derived (cold-adapted or temperature-sensitive) strains. Randolph teach that attenuated RSV with multiple genetic lesions are more stable and

have a reduced probability of reverting to wild type (see page 3, lines 5-25, and page 7, line 48, through page 8, line 47). Randolph teach intranasal administration of an aerosol containing 10^6 PFU of the infectious RSV for eliciting systemic immunity (see page 3, lines 1-4; page 6, lines 1-10; and page 47, Table 19). The vaccines comprising chimeric viruses and the nucleic acids taught by Randolph anticipate the claimed invention, or in the alternative, one of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have made immunogenic compositions comprising infectious human chimeric subgroup A/subgroup B viruses with the heterologous G gene and further comprising one or more attenuating mutations derived from biologically derived mutant strains based on the teachings of Randolph.

b. Claims 1-12, 16, 18-21, 35, 46-59, and 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy et al. (Virus Research 32:13-36, 1994) in view of Collins et al. (Proc. Natl. Acad. Sci USA, 92:11563-11567, 1995; of record in the IDS filed 02/01/2000).

The claimed invention is as described *supra*.

Murphy et al. teach live attenuated RSV vaccines (see the abstract). Murphy et al. teach that there are two antigenically divergent RSV subgroups and teach that an effective vaccine should protect against both subgroups (see page 15, first full paragraph; page 23, first full paragraph; and page 24, first full and last partial paragraphs). Murphy et al. teach that vaccinia-recombinant viruses expressing either the F or the G glycoprotein of RSV induces almost complete resistance to RSV challenge in mice (see page 20, last partial paragraph) and induces

neutralizing antibodies in monkeys (see page 21, last partial paragraph). Murphy et al. teach RSV vaccines comprising biologically-derived live attenuated host range, cold passaged, and temperature-sensitive mutants. Murphy et al. teach that the biologically-derived attenuated mutants induce an immunogenic response without causing disease (see page 23, second full paragraph; page 25, first full paragraph; and page 26, first full paragraph). Murphy et al. differ from the claimed invention in that they do not teach combining the gene encoding the G glycoprotein from one RSV subgroup with a partial or complete genome of an RSV of the second subgroup and do not teach integrating the mutations from the biologically-derived attenuated strains into the chimeric genome.

Collins et al. teach production of infectious human RSV from cloned cDNA and teach that such an approach makes it possible to introduce defined changes into infectious RSV. Collins et al. teach that production of infectious human RSV with defined changes has " ... immediate applications to the development of live attenuated vaccine strains bearing predetermined defined attenuating mutations" (see the abstract). Collins et al. teach that engineering of the RSV could enhance its immunogenicity and induce protection greater than that provided by natural infection. Collins et al. specifically suggest inclusion of the G protein gene of RSV subgroup B with the genome of RSV subgroup A to "broaden the response to cover a wider spectrum of the relatively diverse subgroup A and B strains present in the human population, allowing a single virus to function as a bivalent vaccine" (see page 11567, the last paragraph).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have made a bivalent immunogenic composition incorporating glycoproteins from both of the RSV subgroups, as taught by either Murphy et al. or Collins et al. with attenuating mutations from biologically-derived RSV strains, as taught by Murphy, for a safe, stable, and efficacious immunogenic composition. One of ordinary skill in the art at the time the invention was made would have also found it *prima facie* obvious to have integrated genes encoding the glycoproteins and attenuating mutations from the biologically-derived strains into a single chimeric virus, as is suggested by Collins et al. Although neither Murphy et al. nor Collins et al. teach administration of 10^3 to 10^6 PFU of the immunogenic composition to the upper respiratory tract, absent some evidence to the contrary, this would constitute routine optimization of a known method.

Conclusion

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Billeter (EPA 0 440 219; of record in the IDS filed 02/01/2000) teaches insertion of a heterologous gene encoding the RSV F and/or G protein into the genome of a negative-stranded RNA virus for generation of infectious chimeric viruses suitable as vaccine preparations (see the abstract, and page 3, lines 6-37 and 40-50).

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
March 13, 2001

Brenda Brumback

Brenda Brumback,
Patent Examiner